IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Breitenbach, A. & Wolff, H.-M.
Serial No.:	**10/630,633**
Filed:	29 July 2003
Title:	HOT-MELT TTS FOR ADMINISTERING ROTIGOTINE
Group Art Unit:	1615
Examiner:	S.T. Tran
Confirmation No.:	9056
Docket No.:	**6102-000068/US**
Client Ref.:	P/Brt/I/5/02

SUBMITTED ELECTRONICALLY VIA EFS-WEB

28 February 2011

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

This paper and its attachments are filed in support of Appellant's Notice of Appeal to the Board of Patent Appeals and Interferences (the Board) from a decision of the U.S. Patent Office. The entire record of the current Application is incorporated herein by reference.

The two months shortened statutory period following the 6 January 2011 filing of the Notice of Appeal expires 6 March 2011.

Authorization is provided to charge the fee for filing a brief in support of the Notice of Appeal under 37 C.F.R. § 41.20(b)(2). No additional fees are believed required in connection with this Appeal Brief. However, the Commissioner is authorized to charge any underpayment or credit any overpayment of fees to Deposit Account No. **08-0750**.

TABLE OF CONTENTS

(A) REAL PARTY IN INTEREST (37 C.F.R. 41.37(c)(1)(i))

The real party in interest in the present Appeal is UCB Pharma GmbH, the Assignee of record in Application Serial No. 10/630,633, having a place of business in Monheim, Germany and a correspondence address of Alfred-Nobel-Strasse 10, 40789 Monheim, Germany. UCB Pharma GmbH is the owner of the entire right, title and interest in the current Application by virtue of an Assignment recorded 26 February 2010, at reel 023985, frame 0822.

(B) RELATED APPEALS AND INTERFERENCES (37 C.F.R. 41.37(c)(1)(ii))

UCB Pharma GmbH (Appellant) knows of no other current appeals or interferences which will directly affect or be directly affected by or which have a bearing on the Board's decision in the present Appeal.

However, Appellant draws the attention of the Board to the Notice of Appeal filed on 19 January 2011 in the related Application U.S. Serial No. 10/523,908, which claims the same priority as the presently appealed application.

(C) STATUS OF CLAIMS (37 C.F.R. 41.37(c)(1)(iii))

Claims 18 and 20-25 stand rejected in the current Application and are the subject of this appeal.

Claims 17 and 19 are canceled.

Claims 1-16, and 26-31 are pending but presently withdrawn (due to restriction requirement imposed on December 2009).

(D) STATUS OF AMENDMENTS (37 C.F.R. 41.37(c)(1)(iv))

No amendment was filed subsequent to final rejection. Pending Claims 1-16, 18 and 20-31 correspond to those submitted on 23 April 2010 in response to the non-final Office Action dated 24 December 2009.

A copy of the pending claims is included in the Claims Appendix attached hereto in accordance with 37 C.F.R. 41.37(c)(1)(viii).

(E) SUMMARY OF CLAIMED SUBJECT MATTER (37 C.F.R. 41.37(c)(1)(v))

All page and line references in this section are to the current Application (U.S. Serial No. 10/630,633 filed on 29 July 2003) as amended and filed on 3 April,2008.

Independent Claim 18 is drawn to a method for preparing a TTS that comprises a rotigotine-containing cement matrix. The method comprises the step of melting and homogenizing components of the cement matrix and rotigotine without solvent in an extruder at a temperature between 70°C and 200°C prior to lamination of the cement matrix. Claim 18 is supported throughout the specification as filed, for example at paragraph [0003] a method for producing a TTS that encompasses a cement matrix containing rotigotine as the active substance, characterized in that, prior to the coating and laminating, the components of the cement matrix are melted and homogenized, without any solvent, at temperatures between 70 and 200°C and preferably between 120 and 160°C in conjunction with [0032] referring to a TTS with a rotigotine-containing cement matrix produced by the hot-melt method employing a process in which the rotigotine is introduced, in molten or preferably in its solid form, into the 70-200°C melt of the solvent-free cement matrix. The rotigotine is introduced in a solvent-free melt that is preferably heated to 100-170°C, desirably to 120-160°C and ideally to 130-150°C, and then processed and cooled within 5 minutes, preferably within 3 minutes and ideally within a maximum of 1 minute after the admixture of the rotigotine.

Claims 20-25 ultimately depend from claim 18 and embody all limitations of Claim 18.

(F) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL (37 C.F.R. 41.37(c)(1)(vi))

1. Rejection of Claims 18 and 20-25 under 35 U.S.C. §103(a) over EP0663431 A2 ("Ulman"), in view of U.S. 2004/0048779 ("Schollmayer").

2. Provisional Rejection of Claims 18 and 20-25 on the ground of nonstatutory obviousness-type double patenting over Claims 28-36 and 41 of co-pending U.S. Serial No. 10/523,908.

(G) ARGUMENT (37 C.F.R. 41.37(c)(1)(vii))

1. Stipulation of Facts

Appellant stipulates to the following facts:

a) Ulman, the primary reference, does not disclose, teach or suggest any specific bioactive agent, much less rotigotine free base, and Ulman's focus is on a hot-meltable adhesive for use with hydrophilic drugs.

b) Schollmayer, the secondary reference, does not disclose a hot-meltable system. In contrast, Schollmayer refers to a method of producing a TTS comprising the mixing of the components in a solvent and drying of the product.

c) Rotigotine is a highly lipophilic compound.

d) At the time of the invention rotigotine was known to be susceptible to oxidation

e) Ulman does not provide any information or data on how lipophilic compounds could be successfully incorporated in a hot-meltable adhesive which is designed for use with hydrophilic drugs.

f) Although Schollmayer reports that rotigotine can be used in a TTS which is produced in a solvent-based process, it is completely silent regarding the use of rotigotine in a hot-meltable adhesive.

2. Rejection under 35 U.S.C. §103(a) over Ulman in view of Schollmayer

2.1 Claims 18 and 20-25

Claims 18 and 20–25 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over EP 0663431 A2 ("Ulman"), in view of U.S. 2004/0048779 ("Schollmayer"). Withdrawal or reversal of this rejection is sought by the present Appeal.

Claim 18 is drawn to a method for preparing a TTS that comprises a rotigotine-containing cement matrix, the method comprising melting and homogenizing components of the cement matrix and rotigotine without solvent in an extruder at a temperature between 70°C and 200°C prior to lamination of the cement matrix.

2.1.1. Not all claimed features are taught or suggested by the cited documents

The Final Office Action (page 5) alleges that it would have been obvious to one ordinary skill in the art to optimize the silicone-based hot melt PSA of Ulman using rotigotine as an active agent in view of the teaching of Schollmayer to obtain the claimed invention".

Ulman as well as Schollmayer fail to teach or suggest all of the claimed features. To establish a *prima facie* case of obviousness, all claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974); In re Wilson, 424 F.2d 1382, 165 USPQ 494 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art").

Claim 18 recites:

> A method for preparing a TTS that comprises a rotigotine-containing cement matrix, the method comprising:
>
> > melting and homogenizing components of the cement matrix and rotigotine without solvent in an extruder at a temperature between 70°C and 200°C prior to lamination of the cement matrix.

The alleged combination fails to teach or suggest all claimed features of Claim 18. In particular, Ulman and Schollmayer, singly or in combination, do not teach (1) homogenization with rotigotine and (2) a hot-melt process without using solvent.

(1) **Homogenizing Rotigotine and Cement Matrix**

As stated in the Final Office Action, Ulman fails to teach the claimed active agent, rotigotine. In fact, Ulman teaches no specific agents, giving no concrete guidance whatsoever as to which specific bioactive agents are suitable for use in the PSA, let alone a method for incorporating such an agent in the PSA without damaging the agent in the process. Ulman describes that a bioactive agent may be incorporated into the hot-melt pressure sensitive adhesive (p. 5, lines 30-31), but this mere statement does not amount to a teaching of specifically homogenizing rotigotine and a cement matrix. Although Schollmayer reports the drug rotigotine, Schollmayer does not cure this deficiency because Schollmayer does not teach that rotigotine can be homogenized with a cement matrix.

(2) **Hot-Melt Rotigotine Process Without Solvent**

Furthermore, Ulman does not teach that rotigotine can be homogenized with a cement matrix in a hot-melt process without solvent. Although, Ulman generally states that their "PSA" does not employ solvents that are found in "traditional" PSAs, Ulman does not expressly teach hot-melt processes without solvent. Additionally, it is incredible to contemplate that an ordinary artisan would believe that Ulman stood for the proposition that any drug could be used in Ulman's hot-melt process, and moreover, any drug could be used without solvent.

Schollmayer does not repair the deficiencies of Ulman. Rather, Schollmayer teaches away from the claimed invention. Schollmayer explicitly recites solvent in each implementation example, for example, methylethyl ketone (paragraph [0053]), ethanol (paragraphs [0057] and [0084]), and heptane (paragraph [0084]). These solvents used in the solvent-based method described in Schollmayer would volatilize at the greater than 100°C temperatures needed to produce the hot-melt PSA of Ulman (p. 5, line 13); methylethyl ketone has a boiling point of 79.6°C, ethanol 78°C, and heptane 98.4°C.

Thus, the alleged combination fails to teach all claimed features, particularly melting and homogenizing the components of the cement matrix and rotigotine without solvent.

Thus, for at least this reason, Claim 18 is not *prima facie* obvious over the alleged combination.

2.1.2. Disclosures are not combinable because teachings are incompatible

Ulman and Schollmayer teach substantially incompatible methods for preparing a transdermal system, and thus the cited publications are not combinable. Ulman describes a method for preparing a hot-melt adhesive, whereas Schollmayer describes a method for preparing a TTS system using solvent. As discussed above, Ulman describes a hot-melt process generally, without teaching any specific agent to be included in a PSA system. And further, Ulman focuses on hydrophilic active agents in contrast to rotigotine which is lipophilic. In fact, Ulman cannot be a primary 103(a) reference against the claimed invention, since it does not recognize technical problems associated with a hot-melt process for rotigotine. Rotigotine is known to be lipophilic and thermally unstable at temperatures above

25°C and prone to oxidative damage at those temperatures. Based on this, one would expect that hot-melt extrusion of rotigotine to fail, because the active agent would be destroyed in the process of making the transdermal therapeutic system (TTS).

Schollmayer discusses a rotigotine-containing TTS, but the solution is significantly different from the claimed invention. It should be noted that the methods described in Schollmayer do not involve preparation of an active-substance-containing a cement matrix nor a hot-melt process. Furthermore, Schollmayer uses solvents to make their rotigotine-containing matrix. See, for example, paragraph [0058] of Schollmayer.

No motivation exists to modify the hot-melt procedure of Ulman with the disparate, solvent-based method of Schollmayer because Ulman does not recognize problems associated with rotigotine and Schollmayer discusses a different process. These two incongruous methods are incompatible, and one having ordinary skill in the art would not have combined these two publications to make a rotigotine-containing TTS using a hot-melt process.

The Final Office Action takes pieces from the cited publications and tries to re-construct the claimed invention in a hindsight manner, without taking into account a critical feature of the claimed invention, *e.g.*, the physical/chemical properties of rotigotine. When a compound is known to be thermally unstable and a claimed process involves treating the compound at a high temperature, it would be logical to analyze why it is obvious or non-obvious to make a final product using a high temperature. However, this aspect is not discussed in the present Office Action at all. Instead, the Examiner asserts that the claimed method is mere "optimization" of existing patch technology. See Final Office Action, p. 5. Appellant respectfully disagrees with the Examiner's view. The present invention cannot constitute "optimization", because there was no known method to be optimized at the time of the present invention. Optimization refers to an act, process, or methodology of making something as fully perfect, functional, or effective as possible, for example, finding a best working temperature range of a known process. Ulman cannot be a basis for optimization because one does not optimize a system by adding an active agent to it. Schollmayer cannot be optimized because it is a totally different method, *i.e.*, a solvent-based method. The system and the active agent are separate and distinct, and are not "optimized" by each others

presence. It is respectfully submitted that the Examiner mischaracterizes the teaching of Schollmayer by not considering its full context. It is irrelevant whether Schollmayer teaches the desirability to incorporate rotigotine in any silicone-based pressure sensitive adhesive system. The relevant teaching is whether such incorporation could be performed at a hot-melt temperature, to which Schollmayer is completely silent.

As shown above, the methods of Ulman and Schollmayer are substantially different and even incompatible. Therefore, it should not be allowed to take pieces from those publications and construct a method with the pieces in a hindsight manner unless the Office provides reasons why such piecemeal items can be combined despite their incompatibility.

Thus, for this additional reason, Claim 18 is not *prima facie* obvious over the alleged combination.

2.1.3. No rationale to modify the cited art to include the missing subject matter

Where the combined references are missing claimed features, a case of obviousness requires an apparent reason, based either on the references themselves or on the general knowledge in the art, by which a skilled artisan would modify the references to include the missing subject matter. See *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) (obviousness includes determining whether there was an apparent reason to combine known elements in the fashion claimed).

As discussed in Section 2.1.2, Ulman does not provide any guidance to a person having ordinary skill to solve problems associated with a hot-melt process for oxidation-sensitive drugs, and thus, cannot be the primary document in this §103(a) rejection. In other words, Ulman is not modifiable to become a hot-melt process for preparing a rotigotine-containing TTS without solvent. Furthermore, the alleged combination, even if combinable, is devoid of any suggestion or appreciation of (1) melting and homogenizing rotigotine and cement matrix and (2) without solvent.

The Final Office Action fails to provide any basis for an ordinary artisan to forgo such use of solvent with rotigotine or include the present melting and homogenizing processes, as required by *In re Kahn*, 441 F3d 977, 78 USPQ2d 1329 (Fed. Cir. 2006) ("rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must

be some articulated reasoning to support the legal conclusion of obviousness"). In contradistinction, the present specification illustrates several advantages and benefits over solvent-based systems (see specification, paragraph [0008]). Absent the articulated reasoning required by *In re Kahn* and by *KSR*, the combination of Ulman and Schollmayer cannot support a presumption of *prima facie* obviousness. No suggestion is made in either Ulman or Schollmayer that rotigotine would be stable in the claimed TTS production method.

Thus, for this additional reason, Claim 18 is not *prima facie* obvious over the alleged combination.

2.1.4. Predictability of outcome required for *prima facie* obviousness is lacking

The Examiner has not addressed Appellant's evidence of unpredictability in both the Final Office Action dated 7 July 2010 and the Advisory Action dated 29 December 2010 according to the requirement in MPEP 707.07(f) to answer all material traversed. Therefore, Appellant has repeated this argument herein for consideration. Rotigotine is known to be very susceptible to oxidation; that is, rotigotine tends to decompose at a higher temperature in oxidative fashion. Thus, no one would have been able to predict that rotigotine would lend itself to processing by the present hot-melt methods at a temperature up to 160°C. Further, it could not have been predicted that rotigotine would be released from matrices prepared in this way in a continuous fashion and at a therapeutically desirable rate (specification, paragraph [0026]). However, it was surprisingly discovered by the present inventors that, despite rotigotine's known susceptibility to oxidation, rotigotine actually is compatible with hot-melt technique. Rotigotine remains stable on melting and is present in the resulting matrix at a purity level that is routinely better than 98% and generally over 99%, as measured at 220 nm and 272 nm by HPLC (specification, paragraph [0027] and Tables 2, 3 and 4). It should be understood that high drug-loaded solid dispersion with high drug dissolution enhancement is not an easy task since the drug presented in such a system has high crystallinity. Despite these difficulties, Appellant has provided a method for preparing a TTS that comprises a rotigotine-containing cement matrix with a high concentration of rotigotine and with high drug dissolution enhancement. Also, the claimed method enables a cement matrix to include higher rotigotine concentrations than other layers prepared by solvent-based processes.

Furthermore, the present invention provides improved safety and processing times (specification, paragraph [0030]).

None of these advantageous outcomes were predictable from each of Ulman and Schollmayer or any combination thereof. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art (MPEP 2143.01.III, citing *KSR*, *supra*).

For at least this reason, Claim 18 is not *prima facie* obvious over the cited art.

2.1.5. Conclusion

In sum, the Office has not established a presumption of *prima facie* obviousness of Claim 18 directed to a method for preparing a rotigotine-containing TTS because (1) the alleged combination does not teach all claimed features; (2) the cited publications are not combinable because teachings are incompatible; (3) there is no rationale to modify the cited art to include the missing subject matter; and (4) predictability of outcome required for a finding of *prima facie* obviousness is lacking.

2.2. Claims 20-25

Claims 20-25 depend directly or indirectly from Claim 18 and therefore embody all limitations of Claim 18. For at least all the reasons set forth above, the Examiner has failed to establish a presumption of *prima facie* obviousness of Claim 18 over Ulman in view of Schollmayer. Therefore all claims dependent therefrom, including Claims 20-25 are patentable over Ulman in view of Schollmayer for at least the same reasons.

3. Provisional Rejection of Claims 18 and 20-25 on the ground of nonstatutory obviousness-type double patenting over Claims 28-36 and 41 of co-pending U.S. Serial No. 10/523,908.

Claims 18 and 20–25 stand provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 28–36 and 41 of co-pending application Serial No. 10/523,908. The rejection is provisional because the allegedly conflicting claims of co-pending application Serial No. 10/523,908, *i.e.*, Claims 28-

36 and 41, have not yet been patented. Appellant may elect to argue to overcome this ground of rejection or to provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the co-pending application issues as a patent.

As articulated in Appellant's 23 April 2010 Response, it is respectfully pointed out that the pending claims under consideration, i.e., Claims 18 and 20-25, are all directed to a method of preparing a TTS, whereas the pending claims under consideration of copending application Serial No. 10/523,908, i.e., Claims 28-36 and 41, are all drawn to a TTS (i.e., an article invention). Therefore, the provisional obviousness-type double patenting rejection is no longer applicable to this application in view of the bifurcated subject matter claimed in each application.

Withdrawal or reversal of the present rejections is respectfully requested.

Respectfully submitted,

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(H) Claims Appendix (37 C.F.R. 41.37(c)(1)(viii))

1. (Withdrawn) A transdermal therapeutic system (TTS) comprising an active-substance-containing cement matrix, wherein the cement matrix comprises a hot-meltable adhesive in which the active substance is dispersed and melted using a hot-melt process, and wherein the active substance is rotigotine and is partly or completely dissolved in the adhesive.

2. (Withdrawn) The TTS of claim 1, wherein the active-substance-containing cement matrix is produced by preparing a solvent-free melt of the cement matrix and metering the rotigotine into the solvent-free melt at a temperature between 70°C and 200°C.

3. (Withdrawn) The TTS of claim 1, wherein the hot-meltable adhesive comprises an amine-resistant silicone adhesive and, in mixture therewith, at least one pharmaceutically acceptable softener.

4. (Withdrawn) The TTS of claim 3, wherein the at least one softener is an organic wax.

5. (Withdrawn) The TTS of claim 3, wherein the at least one softener is ceresine or ozokerite.

6. (Withdrawn) The TTS of claim 1, wherein the cement matrix comprises 4–40 weight % rotigotine.

7. (Withdrawn) The TTS of claim 1, wherein the cement matrix comprises 9–30 weight % rotigotine.

8. (Withdrawn) The TTS of claim 1, wherein the cement matrix comprises 20–40 weight % rotigotine.

9. (Withdrawn) The TTS of claim 1, wherein the rotigotine is present in free-base form.

10. (Withdrawn) The TTS of claim 1, wherein the active-substance-containing cement matrix further comprises an internal-phase component selected from the group consisting of
    (a) hydrophilic and amphiphilic polymers and mixtures thereof with pharmaceutically acceptable softeners,

(b) hydrophilic and amphiphilic copolymers and mixtures thereof with pharmaceutically acceptable softeners,

(c) condensates of glycerin and fatty acids,

(d) condensates of glycerin and polyols, and

(e) mixtures of components (a)–(d).

11. (Withdrawn) The TTS of claim 1, wherein the active-substance-containing cement matrix further comprises at least one internal-phase component selected from the group consisting of polysaccharides, substituted polysaccharides, polyethylene oxides, polyvinyl acetates, polyvinyl pyrrolidones, copolymers of polyvinyl pyrrolidone and polyvinyl acetate, polyethylene glycol, polypropylene glycol, copolymers of ethylene and vinyl acetate, glycerin-fatty acid esters and mixtures of polyvinyl alcohol with glycerin.

12. (Withdrawn) The TTS of claim 1, wherein the cement matrix comprises

(a) 50–99 weight % of a hot-meltable adhesive,

(b) 4–40 weight % of rotigotine,

(c) 0–40 weight % of an internal-phase component, and

(d) 0–10 weight % of other adjuvants.

13. (Withdrawn) The TTS of claim 12, wherein the hot-meltable adhesive is an EVA adhesive, an SXS adhesive, or a mixture of (i) 70–99 weight % of an amine-resistant silicone adhesive and (ii) 1–30 weight % of a pharmaceutically acceptable softener.

14. (Withdrawn) The TTS of claim 12, wherein the rotigotine is present in an amount effective, upon application of the TTS on skin of a human patient, to induce an average plasma concentration of 0.4 to 2 ng/ml rotigotine in the patient for a period of at least 5 days following said application.

15. (Withdrawn) The TTS of claim 14, wherein the rotigotine is present in an amount effective to induce an average plasma concentration of 0.4 to 2 ng/ml rotigotine in the patient for a period of at least 7 days following said application.

16. (Withdrawn) The TTS of claim 1, wherein the rotigotine is present in an amount

effective, upon application of the TTS on skin of a human patient, to provide transport of rotigotine through the skin at a steady-state flux rate of 200–300 μg per hour.

17. (Canceled)

18. (Previously presented) A method for preparing a TTS that comprises a rotigotine-containing cement matrix, the method comprising:

melting and homogenizing components of the cement matrix and rotigotine without solvent in an extruder at a temperature between 70°C and 200°C prior to lamination of the cement matrix.

19. (Canceled)

20. (Previously presented) The method of Claim 18, wherein the melting and homogenizing is a two-step process comprising:

melting and homogenizing components of the cement matrix other than rotigotine without solvent, and

introducing rotigotine at a temperature between 70°C and 200°C, into the melted cement matrix.

21. (Previously presented) The method of Claim 20, wherein the temperature is between 120°C and 160°C.

22. (Previously presented) The method of Claim 20, wherein the rotigotine is introduced in solid state into the melted cement matrix.

23. (Previously presented) The method of Claim 20, wherein the rotigotine in the cement matrix has a purity level of at least 98% as measured by HPLC at 220 nm and 272 nm.

24. (Previously presented) The method of Claim 18, wherein the temperature is between 120°C and 160°C.

25. (Previously presented) The method of Claim 20, wherein the rotigotine in the cement matrix has a purity level of at least 98% as measured by HPLC at 220 nm and 272 nm.

26. (Withdrawn) The TTS of claim 1, wherein the rotigotine is present in a therapeutically

effective amount for treatment of a disease associated with a dopamine-metabolism disorder in a human patient, by application of the TTS on skin of the patient.

27. (Withdrawn) The TTS of claim 26, wherein the disease associated with a dopamine-metabolism disorder is Parkinson's disease.

28. (Withdrawn) The TTS of claim 26, wherein the disease associated with a dopamine-metabolism disorder is restless leg syndrome.

29. (Withdrawn) A method for treating a disease associated with a dopamine-metabolism disorder in a human patient, comprising applying to skin of the patient a TTS of claim 1 in a therapeutically effective amount.

30. (Withdrawn) The method of claim 29, wherein the disease associated with a dopamine-metabolism disorder is Parkinson's disease.

31. (Withdrawn) The method of claim 29, wherein the disease associated with a dopamine-metabolism disorder is restless leg syndrome.

(I) Evidence Appendix (37 C.F.R. 41.37(c)(1)(ix))

None.

(J) Related Proceedings Appendix (37 C.F.R. 41.37(c)(1)(x))

None.